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Docket No.: 50229-194

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

Kenneth B. AIN, et al. :

Serial No.: 09/606,042 : Group Art Unit: 1614

Filed: June 29, 2000 : Examiner: Rawlings

For: IODIDE UPTAKE RESTORATION IN THYROID CANCER

#10
JM
12/21/01

RESPONSE TO 30 DAY LETTER

Commissioner for Patents
Washington, DC 20231

Sir:

Responsive to the 30 Day letter dated November 23, 2001, a response being due on or before December 23, 2001, reconsideration is requested in view of the following remarks.

This Response is supplemental to the September 5, 2001, response, which is incorporated herein by reference in its entirety.

In the 30 Day letter, it was asserted that Applicants' representative had failed to respond to section 11 of the office action of May 9, 2001, but that the September 5 response appeared to be a bona fide attempt to respond. Applicants affirm that the September 5 response was intended to be a bona fide response to the May 9 office action.

Applicants respectfully submit that, in view of the amendment set forth in the September 5 response, and in view of the remarks set forth therein with

respect to section 10, the rejection set forth in section 11 has been substantially traversed. However, given the additional opportunity to respond to the section 11 rejection, Applicants provide the following remarks in favor of the patentability of claim 16.

In the May 9 office action, section 11, claim 16 was rejected under 35 U.S.C. § 112, first paragraph as lacking enablement in the originally filed specification. Applicants traverse this rejection. The basis of the rejection, set forth on page 7 of the office action, is apparently that the claims are of undue breadth, however the questions raised within the body of the Examiner's remarks appear directed toward the question of utility. While the examiner acknowledged that the disclosure is enabling with regard to a hypothetical claim limited to a single carcinoma cell line, i.e. NPA'87, and a single therapeutic agent, i.e. 5-azacytidine, the Examiner concluded that the disclosure "does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims." The general tenor of the rejection, as discussed below, appears however to question the general utility of the claimed method. Applicants traverse this rejection.

Applicants first note that claim 16, which is the subject of section 11, is narrower in scope than claim 1, which was the subject of a § 112, first paragraph rejection in section 10. Applicants therefor submit that claim 16 is logically enabled within the meaning of § 112, first paragraph for the reasons set forth in Applicants' response to the rejection of claims 1 et seq. in section 10 of the

September 5 response. However, Applicants provide the following additional remarks in response to the rejection of claim 16 set forth in section 11.

The United States Court of Appeals for the Federal Circuit requires the Patent and Trademark Office to bear the initial burden of going forward on a rejection under 35 U.S.C. § 112, first paragraph. See In re Brana, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)(quoting In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. Id. The Examiner has raised several objections to Applicants' asserted utility, however Applicants submit that the sum total of these objections would not raise a sufficient doubt in the mind of the hypothetical person of skill in the art sufficient for such person to question the asserted utility. Accordingly, Applicants submit that the § 112, first paragraph, rejection of claim 16 is untenable.

In construing claim 16, the Examiner concludes that, when "given the broadest, reasonable interpretation, the claims read on a method of treating a patient diagnosed with dedifferentiated thyroid cancer." Applicants wish to point out that this construction of claim 16 appears to broaden the scope of the claim well beyond its intended scope. While the claim indeed may read on a method of treating a patient, the treatment is for "restoring iodide transport to dedifferentiated thyroid cancer cells." Implicit in this language is the requirement that the type of thyroid cancer cells are have lost iodide transport ability and are

susceptible to restoration of the same. The disclosure contains examples of cell lines that are susceptible to restoration of iodide transport due to treatment with demethylating agent, and the clinician viewing these results would have all the ammunition needed to determine whether a putative patient would be a good candidate for the claimed therapeutic method, and if so, what dosages should be used. The examiner has provided no evidence whatsoever to dispute the asserted utility. Accordingly the § 112, first paragraph rejection is untenable and should be withdrawn.

The Examiner criticized the stated utility of the present invention in several regards, which are addressed below.

First, the Examiner stated that there is insufficient guidance and exemplification in view of the unpredictability in the cancer therapy art and the obvious limitations of the claimed method such that one could not practice the claimed invention commensurate with the scope of the claims. Applicants submit that the Examiner's assessment is partially predicated on an unduly broad reading of claim 16, as discussed above. In particular, the "obvious limitations" noted by the Examiner have been taken into account in the wording of claim 16, where it is stated that the method is for "restoring iodide transport," not a method of treating all kinds of cancers in the human body. Applicants submit that whatever limitations there may be will be duly recognized by the person having skill in the art, who will be more than capable of making allowances for these limitations in plotting a course of therapy. After all, if the limitations are indeed "obvious," to anyone, they must be obvious to the person having skill in the art.

And armed with the knowledge provided by Applicants' disclosure, the person having skill in the art will be well-prepared to tailor the course of treatment to the needs of the particular patient.

The Examiner raises the objection that there are numerous mechanisms by which expression of a gene encoding the sodium/iodide symporter may be repressed, as Applicants noted at page 8, lines 16-19 of their disclosure. The Examiner concludes that "not all patients subjected to treatment with a demethylating agent, according to the claimed method, will be expected to benefit...." The Examiner seems to be saying that if there is even one inoperative embodiment within the scope of Applicants' claim, the claim is not enabled. This is a legal standard with which the undersigned is unfamiliar. The more familiar legal standard is that of "objective enablement," which was set forth in Marzocchi, and reiterated in Brana, supra. In Marzocchi, the examiner had objected to the scope of a claim, ostensibly because of the possibility of inoperative embodiments. While the court agreed that potentially some of the embodiments might be inoperative, the court accorded this potential no moment in discerning the scope of enablement. 169 USPQ at 370. In the present case, as in Marzocchi, the person having skill in the art will recognize the limitations in the claimed method, such as they are, and will be able to readily avoid inoperative embodiments using ordinary skill. Id. In particular, the present disclosure presents testing of a number of human-derived thyroid cancer cell lines, against a number of demethylating agents, and presents results for those tests. The person having skill in the art would be more than capable of

conducting similar testing to determine both whether a patient would likely respond to the claimed method, and if so what dosage of which demethylating agent to use.

The Examiner also apparently objects to the lack of human testing of the claimed method. Again, Applicants are aware of no authority, and the Examiner has provided none, to the effect that human testing is a requirement of § 112, first paragraph. Indeed, In re Brana says the exact opposite. After the examiner made a rejection under § 112, first paragraph alleging that "cancer" was too broad and diffuse a term to be enabled by the applicants' disclosure (which lacked human clinical data), and after the Board concurred in this judgment, the Court reversed, stating *inter alia* that "the purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking," and that "applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of § 112." 34 USPQ2d at 1441. There, as here, the examiner had made the legal mistake of thrusting the initial burden of proof upon the applicants. Additionally, the examiner in Brana failed to accord sufficient weight to the data set forth in the disclosure tending to validate the claimed method, choosing instead to confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". 34 USPQ2d at 1442.

The examiner also criticized the claimed method based on the unsupported allegation that "the cost of treatment may actually outweigh any

benefit the treatment may offer." Again, Applicants note In re Brana, 34 USPQ2d 1436, 1442, for the correct statement of the law, which is that it is the province of the United States Food and Drug Agency, not the PTO, to determine the relative costs and benefits of a particular therapy.

The Examiner attempts to support the cost-benefit criticism with a reference to Thomas et al., which the examiner alleges to teach that 5-azacytidine causes thyroid tumors. The examiner goes on to state that "obviously, it makes little sense to treat a patient diagnosed with thyroid cancer with an agent that causes further production of thyroid tumors," and that "the specification provides no guidance with regard to this issue." Applicants dispute both the Examiner's premise and the conclusion.

The premise that "it makes little sense" to treat a person having a tumor with a potential carcinogen is belied both by the common knowledge that "dose makes the poison" (i.e. at lower doses an anti-cancer drug, such as paclitaxel, may be therapeutically beneficial, whereas at higher doses, the same may be harmful or even lethal), and by the Thomas et al. reference itself. Applicants point, *inter alia* to page 1040 of Thomas et al., where, in the last partial paragraph, it is stated that "in the doses used, I^{131} was more effective [in causing tumors] than" 5-azacytidine. It is noted that the point of the Thomas et al. reference was stated to be to induce thyroid tumors in mice. It is also noted that I^{131} is a common therapeutic agent, not only for thyroid tumors in humans, but also for treatment of other thyroid maladies, such as hyperthyroidism. By the Examiner's logic, however, I^{131} should be entirely useless as a therapeutic agent.

That I^{131} is not useless as a human thyroid anti-hyperplasia therapeutic agent, defeats the conclusion that demethylating agents, such as 5-azacytidine, are useless as therapeutic agents. At the very least, it calls into question the Examiner's unsupported statement that "it makes little sense" to treat a person having a tumor with a potential carcinogen. Not only does it make sense, it is done all the time.

The disclosure provides ample guidance for the skilled artisan to practice the invention. In particular, the disclosure shows that 0.5 μM 5-azaC fails to produce the desired response, but 1.0 μM 5-azaC elicits the desired response. In general, the artisan will choose the lowest therapeutic dose, which the artisan will be able to derive from the results set forth in the disclosure. Titration of the effect to achieve the desired response, while avoiding untoward side effects, is also well within the skill of the artisan in this field. The Examiner has provided no evidence to support the notion that the skilled clinician would be unable to predict useful doses of the demethylating agents based on the disclosed data.

The examiner notes the alleged cytotoxicity of many demethylating agents as evidence contradicting the claimed utility. In fact, most anti-cancer drugs are highly cytotoxic, which has not entirely limited their desirability or therapeutic usefulness. For instance, paclitaxel is both a useful anti-cancer drug and a highly cytotoxic chemical, which produces adverse side effects ranging from nausea to alopecia to death. Applicants submit that the cost-benefit analysis regarding any therapeutic drugs, and in particular the therapeutic methods at

issue, is properly left in the province of the FDA (see Brana, supra), and ultimately the treating physician.

The remainder of the Examiner's arguments amount to prolix recitation of reasons why (1) the present method may be contraindicated in some patients or (2) the present method may not work with all thyroid cancers (such as anaplastic thyroid cancers). Applicants submit that these arguments have been fully addressed above. First, it is not necessary that Applicants present clinical testing data to support their presumptively believable utility. See Brana, supra. Second, it is not necessary that all embodiments embraced by the claims be operative. See Marzocchi, supra.

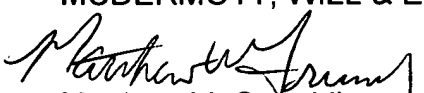
Applicants submit that the foregoing arguments, when taken together with the entirety of the September 5 response, are fully responsive to the Examiner's rejection of section 11, and that claim 16 is fully enabled within the meaning of § 112, first paragraph.

Applicants respectfully request withdrawal of the rejection of claim 16 under 35 U.S.C. § 112, first paragraph and allowance of the pending claims.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

MCDERMOTT, WILL & EMERY



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